

Design, Synthesis and Biological Evaluation of Some Novel 3-Methylquinoxaline-2-Hydrazone Derivatives

Taiwo FO¹, Obuotor EM², Olawuni IJ², Ikechukwu DA¹ and Iyiola TO¹

¹Department of Chemistry, Obafemi Awolowo University, Nigeria

²Department of Biochemistry, Obafemi Awolowo University, Nigeria

Abstract

Alzheimer's disease is a chronic and progressive neurodegenerative disease which occurs due to lower levels of acetylcholine neurotransmitters, and results in a gradual decline in memory and other cognitive processes. Acetylcholinesterase and butyrylcholinesterase have been reported to be the primary regulators of the acetylcholine levels in the brain. Evidence shows that acetylcholinesterase activity decreases in Alzheimer's disease, while activity of butyrylcholinesterase elevates in advanced Alzheimer's disease, which suggests a key involvement of butyrylcholinesterase in acetylcholine hydrolysis during Alzheimer's disease symptoms. In order to sustain the level of remaining acetylcholine, acetylcholinesterase and butyrylcholinesterase inhibitors may be used. Therefore, inhibiting the activity of butyrylcholinesterase may be an effective way to control Alzheimer's disease associated disorders. In this study, eleven 3-methylquinoxaline-2-hydrazones were synthesized from the reactions of 3-methylquinoxaline-2-hydrazine with different substituted aromatic ketones and aromatic aldehyde. All the newly synthesized compounds have been characterized on the basis of IR, ¹H-NMR and ¹³C-NMR spectral data as well as physical data. All the synthesized compounds were biologically evaluated against cholinesterases (acetylcholinesterase and butyrylcholinesterase). Compounds 2-12 were found to be a good selective inhibitor for acetylcholinesterase and butyrylcholinesterase. Among the series, compounds 6 (IC₅₀=170 ± 30 µg/mL) and 10 (IC₅₀=180 ± 10 µg/mL) were found to be the most active inhibitors against acetylcholinesterase, while compounds 2 (IC₅₀=780 ± 10 µg/mL), 5 (IC₅₀=550 ± 10 µg/mL) and 6 (IC₅₀=790 ± 10 µg/mL), were found to be most active inhibitor against butyrylcholinesterase. The IC₅₀ values for all the synthesized compounds were lower than standard, eserine (IC₅₀=70 ± 20 µg/mL). Their considerable acetylcholinesterase and butyrylcholinesterase inhibitory activities makes them a good candidate for the development of selective acetylcholinesterase and butyrylcholinesterase inhibitors.

Keywords: Alzheimer's disease; Acetylcholine; 3Methylquinoxaline; Acetylcholinesterase; Butyrylcholinesterase; Eserine; Hydrazones

Introduction

Heterocyclic compounds represent an important class of biological active molecules [1]. Specifically those containing quinoxaline derivatives have evoked considerable attention in recent years. Quinoxaline, or 1,4-benzo[pyrazine] is an important structural unit among nitrogen-containing heterocyclic compounds. Quinoxalines are, in general, easy to prepare and numerous derivatives have been reported in the literature because of their biological activity, specifically as antimicrobial [2-8], antibacterial [9-11], anti-cancer [12], anti-aminoceptive [13], anti-inflammatory [14,15] anti-viral [16-18], antimalaria [19] agents. They possess well known biological activities including AMPA/GlyN receptor antagonist [20], antihistaminic agents [21], anti-trypanosomal activity [22], anti-herpes, trypanocida, antiplasmodial activity [23], Ca²⁺ uptake/release inhibitor [24], and inhibitor of vascular smooth muscle cell proliferation. Quinoxaline derivatives constitute the basis of many insecticides, fungicides, herbicides, as well as being important in human health and as receptor antagonists. Although rarely described in nature, synthetic quinoxaline moiety is a part of number of antibiotics such as echinomycin [25], levomycin and actinomycin which are known to inhibit the growth of Gram-positive bacteria and also active against various transplantable tumors [5,26]. In addition, quinoxaline derivatives are reported for their application in dyes, efficient electroluminescent materials, organic semiconductors, and DNA cleaving agents [27].

Alzheimer's disease is a common form of dementia in which severe loss of cholinergic cell occurs, which subsequently leads to low levels of the neurotransmitter acetylcholine in brain. Acetylcholinesterase is the key enzyme involved in the metabolic hydrolysis of acetylcholine. This observation led to the introduction of the acetylcholinesterase inhibitors

to prolong the duration of action of acetylcholine [28]. Another enzyme, butyrylcholinesterase, expressed in selected areas of the central and peripheral nervous systems, is also capable of hydrolyzing acetylcholine [29]. The management of Alzheimer's disease has been a long-standing challenge and area of interest [30]. Despite the long history of the disease, there are currently very few drugs used clinically for the management of Alzheimer's disease [31]. This work was therefore designed to synthesize new quinoxaline compounds carrying the hydrazone functional group at the 2-position, elucidate their structures, in addition the compounds were evaluated against cholinesterases (acetylcholinesterase and butyrylcholinesterase).

Materials and Methods

Melting points were determined with open capillary tube on a Gallenkamp (variable heater) melting point apparatus and were uncorrected. Infrared spectra were recorded as KBr pellets on a Buck Spectrometer. The ¹H-NMR and ¹³C-NMR was run on a Bruker 600 MHz spectrometer (δ in ppm relative to Me₄Si) at the Department of Chemistry, Portland state University, Portland USA. The purity of the

*Corresponding author: Taiwo FO, Department of Chemistry, Obafemi Awolowo University, Nigeria, Tel: +234(0)7065536132; E-mail: oftaiwo@yahoo.co.uk

Received: May 08, 2017; Accepted: May 22, 2017; Published: May 27, 2017

Citation: Taiwo FO, Obuotor EM, Olawuni IJ, Ikechukwu DA, Iyiola TO (2017) Design, Synthesis and Biological Evaluation of Some Novel 3-Methylquinoxaline-2-Hydrazone Derivatives. Organic Chem Curr Res 6: 181. doi: [10.4172/2161-0401.1000181](https://doi.org/10.4172/2161-0401.1000181)

Copyright: © 2017 Taiwo FO, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

compounds was routinely checked by TLC on silica gel G plates using n-hexane/ethyl acetate (1:1, v/v) solvent system and the developed plates were visualized by UV light. All reagents used were obtained from Sigma-Aldrich Chemical Ltd.

Synthesis of 3-methylquinoxaline-2(1H)-one

O-phenylenediamine (20 g 0.10 M) and ethyl pyruvate (22 g 0.10 M) in 200 ml of absolute ethanol was heated for 30 minutes on oil bath. The reaction mixture was allowed to cool to give some silvery white crystals which were collected by filtration, washed and purified by recrystallization from ethanol.

Synthesis of 2-hydrazinyl-3-methyl-1,2-dihydroquinoxaline 1

3-methyl quinoxalin-2-(1H)-one (10 g, 0.0625 mol.) was added to a mixture hydrazine hydrate and 20 ml of water. The resulting mixture was refluxed for 4 hour. The reaction mixture was allowed to cool to room temperature to afford a brownish-yellow solid precipitate which was filtered, dried and recrystallized from ethanol.

General procedure for the reaction of 2-hydrazinyl-3-methyl-1,2-dihydroquinoxaline with substituted aromatic ketones

2-hydrazinyl-3-methyl-1,2-dihydroquinoxaline (1.0 g, 5.67 mmol) and various substituted aromatic ketones (5.67 mmol) were added to glacial acetic acid (10 ml) in a round bottom flask and refluxed at 120°C for 3 hours. The reaction mixture was cooled and poured into crushed ice with continuous stirring to obtain a solid product which was filtered and dried. Recrystallization from DMF/water afforded the hydrazones 2-11.

General procedure for the reaction of 2-hydrazinyl-3-methyl-1,2-dihydroquinoxaline with aromatic aldehydes

2-hydrazinyl-3-methyl-1,2-dihydroquinoxaline (1.0 g, 5.67 mmol) and naphthaldehyde (5.67 mmol) were added to glacial acetic acid (10 ml) in a round bottom flask and refluxed at 120°C for 3 hours. The reaction mixture was cooled and poured into crushed ice with continuous stirring to obtain a solid product which was filtered and dried. Recrystallization from DMF/water afforded 1-(2-methylquinoxalin-3-yl)-2-((naphthalen-1-yl)methylene)hydrazine 12.

Spectral data synthesized compounds

3-methylquinoxaline-2(1H)-one: % yield: 76.44%; Melting point: 245-247°C lit. 246°C [15-16]; IR KBr (cm⁻¹): 3103 (C-H sp² str.), 1602 (C=C aromatic str.), 1660 (C=N str.), 2866 (C-H sp³ str.), 3462 (NH str.), 1568 (N-H bend), 1690 (C=O str.).

¹H-NMR (DMSO-d₆): 10.66 (broad s, 1H, quinoxaline NH), 8.27(J=8, 2) (d, 1H, aromatic protons); 7.47(J=8, 2) (t, 1H, aromatic protons); 7.31(J=8, 2) (t, 1H, aromatic protons); 7.09(J=8, 2) (d, 1H, aromatic protons); 2.07 (s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 156 ppm, 154 ppm (C=O), 133 ppm, 131 ppm, 129 ppm, 125 ppm, 1253 ppm, 115 ppm, 21 ppm.

2-hydrazinyl-3-methyl-1,2-dihydroquinoxaline (1): % yield: 76.44%; Melting point: 318-320°C; IR KBr (cm⁻¹): 3448 (N-H str.), 3308 (N-H₂ str.), 3007 (N-H₂ str.), 2966 (C-H sp² str.), 2898 (C-H sp³ str.), 1568 (N-H bend), 1665 (C=N str.)

¹H-NMR (DMSO-d₆): 8.46 (broad s, 1H, hydrazine NH), 7.94(J=8, 2) (d, 1H, aromatic protons); 7.82(J=8, 8, 2) (d, 1H, aromatic protons); 7.78(J=8, 8, 2) (t, 1H, aromatic protons); 7.67(J=8, 8, 2) (t, 1H, aromatic protons); 4.59 (broad s, 2H, hydrazine NH₂) 2.42 (s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 163 ppm, 145 ppm, 135 ppm, 127 ppm, 125 ppm, 124 ppm, 17 ppm.

(E)-2-methyl-3-(2-(1-phenylethylidene)hydrazinyl)quinoxaline (2): % yield: 75.40%; Melting point: 252-254°C; IR KBr (cm⁻¹): 3435 (N-H str.), 2899 (C-H sp³ str.), 1602 (C=C aromatic str.), 1665 (C=N str.), 1564 (N-H bend), 1008 (N-N str.).

¹H-NMR (DMSO-d₆): 10.43 (broad s, 1H, hydrazine NH), 7.95(d, 2H, aromatics protons), 7.93 (d, 1H, aromatic proton); 7.90 (d, 1H, aromatic proton); 7.80 (d, 1H, aromatic proton); 7.76 (t, 1H, aromatic protons); 7.55 (t, 1H, aromatics proton), 7.53 (t, 2H, aromatics protons), 2.94 (s, 3H, methyl proton), 2.40 (s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 168 ppm, 163 ppm, 145 ppm, 137 ppm, 135 ppm, 131 ppm, 127 ppm, 125 ppm, 124 ppm, 17 ppm.

(E)-2-(2-(1-(4-bromophenyl)ethylidene)hydrazinyl)-3-methylquinoxaline (3): % yield: 78.40%; Melting point: 254-256°C; IR KBr (cm⁻¹): 3442 (N-H str.), 2910 (C-H sp³ str.), 1605 (C=C aromatic str.), 1664 (C=N str.), 1598 (N-H bend).

¹H-NMR (DMSO-d₆): 10.43 (broad s, 1H, hydrazine NH), 7.60-7.90 (m, 4H, aromatic protons); 7.67 (d, H, aromatic protons); 7.43 (J=8, 8, 2) (t, 1H, aromatic protons); 7.27 (J=8, 8, 2) (t, 1H, aromatic protons); 7.36 (d, 1H, aromatics protons) 2.94 (s, 3H, methyl proton), 2.40(s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 168 ppm, 164 ppm, 145 ppm, 135 ppm, 134 ppm, 133 ppm, 130 ppm, 127 ppm, 125 ppm 124 ppm, 123 ppm, 17 ppm.

(E)-2-(2-(1-(2-fluorophenyl)ethylidene)hydrazinyl)-3-methylquinoxaline (4): % yield: 71.10%; Melting point: 207-209°C; IR KBr (cm⁻¹): 3435 (N-H str.), 2966 (C-H sp³ str.), 1608 (C=C aromatic str.), 1662 (C=N str.), 1564 (N-H bend), 1008 (N-N str.).

¹H-NMR (DMSO-d₆): 10.46 (broad s, 1H, hydrazine NH), 7.60-7.94 (m, 4H, aromatic protons); 7.67 (d, H, aromatic protons); 7.48 (J=8, 8, 2) (t, 1H, aromatic protons); 7.27 (J=8, 8, 2) (t, 1H, aromatic protons); 7.36 (d, 1H, aromatics protons), 2.95 (s, 3H, methyl proton). 2.43 (s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 168 ppm, 159 ppm, 145 ppm, 135 ppm, 134 ppm, 133 ppm, 130 ppm, 127 ppm, 124 ppm, 118 ppm, 17 ppm.

(E)-2-(2-(1-(4-fluorophenyl)ethylidene)hydrazinyl)-3-methylquinoxaline (5): % yield: 85.40%; Melting point: 250-252°C; IR KBr (cm⁻¹): 3458 (N-H str.), 2850 (C-H sp³ str.), 1618 (C=C aromatic str.), 1660 (C=N str.), 1548 (N-H bend).

¹H-NMR (DMSO-d₆): 10.46 (broad s, 1H, hydrazine NH), 7.27 (m, 2H, aromatic protons); 7.67 (d, 1H, aromatic protons); 7.48 (J=8, 8, 2) (t, 1H, aromatic protons); 7.27 (J=8, 8, 2) (m, 1H, aromatic protons); 7.19 (m, 2H, aromatics protons), 2.93 (s, 3H, methyl proton), 2.41 (s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 168 ppm, 165 ppm (C-F), 163 ppm, 145 ppm, 135 ppm, 134 ppm, 133 ppm, 129 ppm, 127 ppm, 124 ppm, 115 ppm, 17 ppm.

(E)-2-(2-(1-(2,4-dibromophenyl)ethylidene)hydrazinyl)-3-methylquinoxaline (6): % yield: 77.35%; Melting point: 183-184°C; IR KBr (cm⁻¹): 3309 (N-H str.), 3103 (C-H sp² str.), 2897 (C-H sp³ str.), 1605 (C=C aromatic str.), 1669 (C=N str.), 1568 (N-H bend).

¹H-NMR (DMSO-d₆): 10.46 (broad s, 1H, hydrazine NH), 7.27 (m,

2H, aromatic protons); 7.67 (d, 1H, aromatic proton); 7.48 (J=8, 8, 2) (t, 1H, aromatic proton); 7.69 (J=8, 8, 2) (m, 2H, aromatic protons); 7.94 (m, 1H, aromatics protons) 2.94 (s, 3H, methyl proton), 2.40 (s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 168 ppm, 164 ppm, 145 ppm, 135 ppm, 134 ppm, 133 ppm, 130 ppm, 127 ppm, 124 ppm, 123 ppm, 17 ppm, 15 ppm.

(E)-4-(1-(2-(3-methylquinoxalin-2-yl)hydrazono)ethyl)aniline (7): % yield: 45.40%; Melting point: 252-254°C; IR KBr (cm⁻¹): 3435 (N-H str.), 2966 (C-H sp³ str.), 1608 (C=C aromatic str.), 1600 (C=N str.), 1564 (N-H bend), 1008 (N-N str.)

¹H-NMR (DMSO-d₆): 10.46 (broad s, 1H, hydrazine NH), 7.27 (m, 2H, aromatic protons); 7.67 (d, 1H, aromatic proton); 7.64 (d, 2H, aromatic proton); 6.88(d, 2H, aromatic protons); 7.94 (m, 1H, aromatics protons), 5.48 (s, 2H, NH₂), 2.94 (s, 3H, methyl proton), 2.40 (s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 168 ppm, 164 ppm, 145 ppm, 135 ppm, 134 ppm, 133 ppm, 130 ppm, 127 ppm, 124 ppm, 123 ppm, 17 ppm, 15 ppm.

2-(2-(3-methylquinoxalin-2-yl)hydrazono)-1H-indene-1,3(2H)-dione (8): % yield: 52.30%; Melting point: 219-221°C; IR KBr (cm⁻¹): 3451 (N-H str.), 1568 (N-H bend), 1608 (C=C aromatic str.), 2900 (C-H sp³ str.), 1590 (C=N str.)

¹H-NMR (DMSO-d₆): 10.45 (broad s, 1H, hydrazine NH), 7.93 (d, 1H, aromatic proton); 7.90 (d, 1H, aromatic proton); 7.80 (d, 1H, aromatic proton); 7.76 (t, 1H, aromatic protons); 7.72(d, 2H, aromatic protons); 7.67 (t, 1H, aromatics proton); 7.61 (t, 1H, aromatics proton), 2.40 (s, 3H, methyl proton)

¹³C-NMR (DMSO-d₆): 163 ppm, 162 ppm (C=O), 145 ppm, 140 ppm, 135 ppm, 127 ppm, 125 ppm, 124 ppm, 122 ppm, 17 ppm.

4,4'-((1E,3Z,5Z,6E)-3-hydroxy-5-(2-(3-methylquinoxalin-2-yl)hydrazono)hepta-1,3,6-triene-1,7-diyl)bis(2-methoxyphenol) (9): % yield: 76.40%; Melting point: 174-179°C; IR KBr (cm⁻¹): 3442 (N-H str.), 2898 (C-H sp³ str.), 1607 (C=C aromatic str.), 1570 (N-H bend), 1662 (C=N str.)

¹H-NMR (DMSO-d₆): 10.45 (broad s, 1H, hydrazine NH), 7.93 (d, 1H, aromatic proton); 7.90 (d, 1H, aromatic proton); 7.80 (d, 1H, aromatic proton); 7.78 (s, 2H, aromatic protons); 6.99(d, 2H, aromatic protons); 6.78 (d, 1H, olefinic proton) 6.86 (d, 1H, olefinic proton); 6.80 (d, 1H, olefinic proton), 5.68 (d, 1H, olefinic proton), 5.33 (d, 1H, olefinic proton); 3.83 (s, 6H, OCH₃ proton); 2.40 (s, 3H, methyl proton)

¹³C-NMR (DMSO-d₆): 174 ppm (C=C-OH), 163 ppm, 156 ppm, 149 ppm, 149 ppm, 147 ppm, 140 ppm, 138 ppm, 135 ppm, 134 ppm, 127 ppm, 125 ppm, 124 ppm, 122 ppm, 119 ppm, 116 ppm, 111 ppm, 87 ppm, 56 ppm (OCH₃), 17 ppm.

(Z)-3-(2-(3-methylquinoxalin-2-yl)hydrazono)indolin-2-one (10): % yield: 65.80%; Melting point: 260-262°C; IR KBr (cm⁻¹): 3435 (N-H str.), 2899 (C-H str.), 1608 (C=C aromatic str.), 1575(C=Nstr.) 1679(C=O str.)

¹H-NMR (DMSO-d₆): 10.45 (broad s, 1H, hydrazine NH), 10.05 (broad s, 1H, hydrazine NH), 7.94 (d, 1H, aromatic proton); 7.92 (d, 1H, aromatic proton); 7.80 (d, 1H, aromatic proton); 7.77 (t, 1H, aromatic protons); 7.73(d, 1H, aromatic protons); 7.68 (d 1H, aromatics proton); 7.61 (t, 1H, aromatics proton); 7.35 (t, 1H, aromatics proton), 2.41 (s, 3H, methyl proton)

¹³C-NMR (DMSO-d₆): 168 ppm (C=O), 163 ppm, 145 ppm, 141

ppm, 135 ppm, 133 ppm, 131 ppm, 129 ppm, 127 ppm, 125 ppm, 124 ppm, 119 ppm, 17 ppm.

2-(2-(1,3-dihydro-2H-inden-2-ylidene)hydrazinyl)-3-methylquinoxaline (11): % yield: 80.20%; Melting point: 249--251°C; IR KBr (cm⁻¹): 3442 (N-H str.), 2968 (C-H sp³ str.), 1602 (C=C aromatic str.), 1570(C=N str.) 1008 (N-N str.)

¹H-NMR (DMSO-d₆): 10.45 (broad s, 1H, hydrazine NH), 7.93 (d, 1H, aromatic proton); 7.90 (d, 1H, aromatic proton); 7.75 (d, 1H, aromatic proton); 7.76 (t, 1H, aromatic protons); 7.45 (d, 2H, aromatics proton); 7.37(t, 2H, aromatics proton), 3.39 (d, 4H, aliphatic protons); 2.40 (s, 3H, methyl proton)

¹³C-NMR (DMSO-d₆): 163 ppm, 155 ppm, 145 ppm, 141 ppm, 135 ppm, 128 ppm, 127 ppm, 125 ppm, 124 ppm, 38 ppm, 32 ppm, 17 ppm.

1-(2-methylquinoxalin-3-yl)-2-((naphthalen-1-yl)methylene)hydrazine (12): % yield: 85.00%; Melting point: 160-161°C; IR KBr (cm⁻¹): 3442 (N-H str.), 2900 (C-H sp³ str.), 1610 (C=C Aromatic str.), 1568(C=N str.)

¹H-NMR (DMSO-d₆): 10.45 (broad s, 1H, hydrazine NH), 8.55 (s, 1H, hydrazino proton); 8.50 (d, 1H, aromatic proton); 7.98 (t, 1H, aromatic proton); 7.93 (d, 1H, aromatic proton); 7.93 (d, 2H, aromatic proton); 7.90 (d, 1H, aromatic proton); 7.77 (t, 1H, aromatic proton); 7.75 (d, 1H, aromatic proton); 7.76 (t, 1H, aromatic protons); 7.45 (t, 2H, aromatics proton), 2.40 (s, 3H, methyl proton).

¹³C-NMR (DMSO-d₆): 163 ppm, 145 ppm, 143 ppm, 135 ppm, 133 ppm, 130 ppm, 128 ppm, 127 ppm, 126 ppm, 125 ppm, 124 ppm, 17 ppm.

Cholinesterase inhibitory assay

AChE and BuChE inhibitions were determined spectrophotometrically using acetyl thiocholine iodide (ATChI) and butyrylthiocholine chloride (BuChCl) as substrate, respectively by the modified method of Ellman et al.

In a 96-well plate was added 240 µl of buffer (50 mM Tris-HCl, pH 8.0) and 20 µl of varying concentrations of the test samples (10, 5, 2.5 and 1.25 mg/ml), 20 µl of the enzyme preparation.

(0.28 U/ml) the reaction mixture was then incubated for 30 min at 37°C, after which 20 µl of 10 mM DTNB was added. The reaction was then initiated by the addition of 20 µl of 25 mM ATChI/BChCl. The rate of hydrolysis of ATChI/BChCl was then determined spectrophotometrically by measuring the change in the absorbance per minute (ΔA/min) due to the formation of the yellow 5-thio-2-nitrobenzoate anion at 412 nm over a period of 4 min at 30 s intervals. A solution of buffer was used as negative control. All assays were carried out in triplicate. Eserine ((-) physostigmine) was used as positive control.

The percentage inhibition (%I) of test sample was obtained using the formula:

$$I(\%) = \left[\frac{(V_0 - V_1)}{V_0} \right] \times 100$$

Where: I (%) = Percentage inhibition

V₁ = enzyme activity in the presence of test sample

V₀ = enzyme activity in the absence of test sample

The synthesized compounds 2-12 were subjected to this test.

Results and Discussion

Chemistry

3-methylquinoxalin-2-one was prepared from the reaction of o-phenylenediamine with ethyl pyruvate in n-butanol (Scheme 1). The

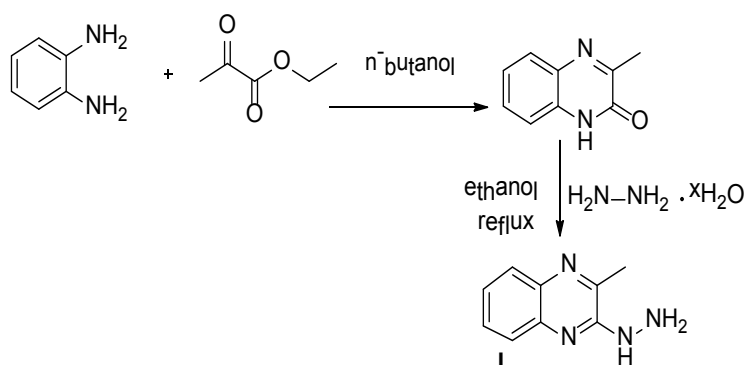
precursor was synthesized from the reaction of 3-methylquinoxalin-2-one with hydrazine hydrate to obtain the 3-methylquinoxalin-2-hydrazine (I). The reaction was carried out by stirring under reflux for four hours. Eleven Nitrogen containing heterocyclic compounds containing 3-methylquinoxaline-2-hydrazone group were synthesized using conventional heating method. These heterocycles include derivatives of Ninhydrin, Curcumin, Isatin, 1-Indanone, Naphthaldehyde and substituted acetophenones (Scheme 2).

The structures of the compounds were partially characterised using Infrared, ^1H and ^{13}C Nuclear Magnetic Resonance spectroscopic methods. All the spectroscopic data confirmed the structures of all the compounds synthesized. The diagnostic bands in the IR spectral for the formation of hydrazones bond $\text{C}=\text{N}$ were observed between 1564 and 1679 cm^{-1} . The NH bands appeared between 3409 and 3451 cm^{-1} , while

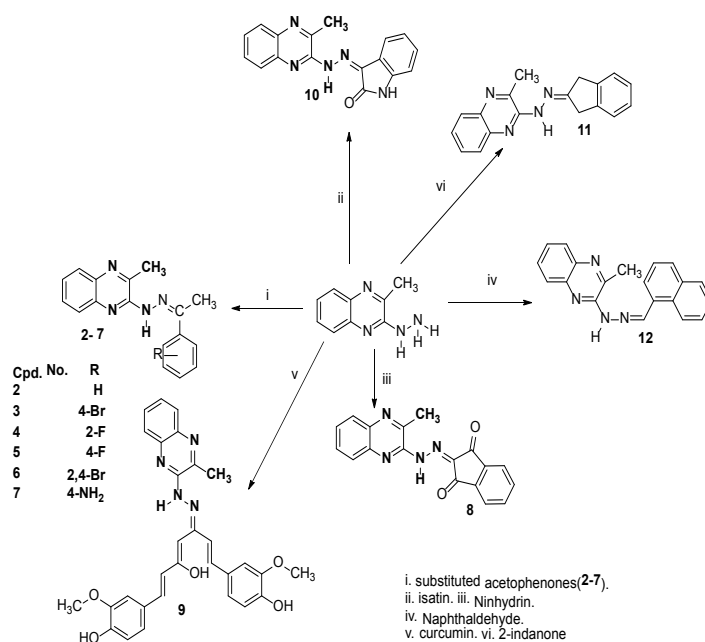
the CH-SP^3 stretching frequency appeared between 2899 and 2969 cm^{-1} . The methyl group appeared in the region of 2.40 and 2.95 ppm in the $^1\text{H-NMR}$ spectral, the azomethine group $\text{CH}=\text{N}$ - proton appeared between 8.55 and 10.46 ppm in the $^1\text{H-NMR}$ spectral.

Biology

Cholinesterase enzymes inhibitory activity: Cholinesterase enzymes inhibitory activity of 2-12 were evaluated using Ellman's assay. Compounds 2-12 were found to be a good selective inhibitor for acetylcholinesterase and butyrylcholinesterase (Table 1). Among the series, compounds **6** ($\text{IC}_{50}=170 \pm 30\text{ }\mu\text{g/mL}$) and **10** ($\text{IC}_{50}=180 \pm 10\text{ }\mu\text{g/mL}$) were found to be the most active inhibitors against acetylcholinesterase, while compounds **2** ($\text{IC}_{50}=780 \pm 10\text{ }\mu\text{g/mL}$), **5** ($\text{IC}_{50}=550 \pm 10\text{ }\mu\text{g/mL}$) and **6** ($\text{IC}_{50}=790 \pm 10\text{ }\mu\text{g/mL}$), were found to be most active inhibitor against butyrylcholinesterase. The IC_{50}



Scheme 1: Reaction of o-phenylenediamine with ethyl pyruvate in n-butanol.



Scheme 2: Synthesis of 3-methylquinoxaline-2-hydrazones (2-12).

| Sample | AChE inhibition, IC ₅₀ (µg /mL) | BChE inhibition, IC ₅₀ (µg /mL) | Selectivity for | |
|---------|--|--|-------------------|-------------------|
| | | | AChE ^a | BChE ^b |
| 2 | 9750 ± 30 | 780 ± 10 | 0.08 | 12.5 |
| 3 | 9980 ± 30 | 1680 ± 70 | 0.17 | 5.94 |
| 4 | 5690 ± 10 | 1620 ± 50 | 0.28 | 3.51 |
| 5 | 9970 ± 40 | 550 ± 10 | 0.06 | 18.13 |
| 6 | 170 ± 10 | 790 ± 10 | 4.65 | 0.22 |
| 7 | 13410 ± 90 | 1260 ± 30 | 0.09 | 10.64 |
| 8 | 1870 ± 30 | 4080 ± 30 | 2.18 | 0.45 |
| 9 | 1500 ± 50 | 5190 ± 30 | 3.46 | 0.29 |
| 10 | 180 ± 10 | 1900 ± 10 | 10.6 | 0.09 |
| 11 | 2670 ± 50 | 3190 ± 10 | 1.19 | 0.83 |
| 12 | 680 ± 50 | 2370 ± 50 | 3.48 | 0.28 |
| Eserine | 70 ± 2.0 | 90 ± 3.0 | 1.28 | 0.77 |

Table 1: IC₅₀ Values for Inhibiting Activities of compounds 2-12 on Cholinesterase Enzymes. A selectivity for AChE is defined as IC₅₀(BChE)/IC₅₀(AChE), b Selectivity for BChE is defined as IC₅₀(AChE)/IC₅₀(BChE).

values for all the synthesized compounds were lower than standard, eserine (IC₅₀ = 70 ± 20 µg/mL). Their considerable acetylcholinesterase and butyrylcholinesterase inhibitory activities makes them a good candidates for the development of selective acetylcholinesterase and butyrylcholinesterase inhibitors. All the compounds were found to be highly selective to acetylcholinesterase and butyrylcholinesterase, respectively.

Alzheimer's disease is a chronic and progressive neurodegenerative disease. The biochemical deficits of this disease are caused by reduced levels of acetylcholine due to substantial reduction in the activity of the enzyme choline acetyltransferase, reduced activity of acetylcholinesterase, and by contrast increased activity of butyrylcholinesterase [32]. In order to sustain the level of remaining acetylcholine, acetylcholinesterase and butyrylcholinesterase inhibitors are used. Thus, compounds 2-12 have potential in the treatment of Alzheimer's disease. Even though they were less active than eserine, they may serve as a potential lead compound for the synthesis of more bioactive derivatives.

In addition, butyrylcholinesterase has been implicated to play important role in the development and progressing of Alzheimer's disease. It cleaves the amyloid precursor protein to β-amyloid that will progress to form α-amyloid plaques, which leads to neurodegeneration. Thus, selective butyrylcholinesterase inhibitor have been reported to prevents the formation of β-amyloid plaques [33] According to Greig et al., selective butyrylcholinesterase inhibitor may be useful in ameliorating a cholinergic deficit in Alzheimer's disease due to increased butyrylcholinesterase activity [34]. Therefore, compound 5 and 6 may serve as a potential lead compound for development of a new class of drug for prevention of the progression of neurodegeneration [35].

Conclusion

It was discovered that the synthetic approach employed for the synthesis of the various 3-methylquinoxalin-2-hydrazones in moderate to excellent yield is highly efficient and successful. All the compounds were found to be highly selective to acetylcholinesterase and butyrylcholinesterase, respectively. Even though their potencies are much lower than eserine, they can be used as starting lead compounds for further optimization by using the docking study on the crystal structures of the cholinesterase enzymes.

Acknowledgements

The Authors would like to thank Professor Reuben H. Simoyi Research Group Laboratory, Portland state University, Oregon, United states of America for supporting this research.

References

- Sakata G, Makino K, Kurasawa Y (1998) Recent Progress in the Quinoxaline Chemistry. *Synthesis and Biological Activity. Heterocycles* 27: 2481-2515.
- Badran M, Abonizid K, Hussein M (2003) Synthesis of certain substituted quinoxalines as antimicrobial agents (Part ii). *Archives of Pharmacy Reserves* 26: 107-113.
- Jaso A, Zarranz B, Aldana I, Monge A (2003) Synthesis of new 2-acetyl and 2-benzoyl quinoxaline-1,4-di-N-oxide derivatives as anti-mycobacterium tuberculosis agents. *European Journal of Medicinal Chemistry* 39: 791-800.
- Hearn MJ, Cynamon MH (2004) Design and synthesis of anti-tuberculars: preparation and evaluation against Mycobacterium tuberculosis of an isoniazid schiff base. *Journal of Antimicrobial Chemotherapy* 55: 185-191.
- Taiwo F, Akinpelu D, Obafemi C (2008) Synthesis and antibacterial activity of some quinoxaline derivatives. *Ife Journal of Science* 10: 19-25.
- Kaurase S, Wadher N, Yeole P (2011) Microwave assisted Synthesis of hydrazone derivatives of quinoxalinone and evaluation of their antimicrobial activity. *International Journal of Universal Pharmacy and Life Sciences* 1: 117-126.
- Aswartha UM, Sreeramulu J, Puna S (2012) Synthesis and antimicrobial activity of a novel series of quinoxaline-2,3-dione derivatives. *International Journal of Advances in Pharmaceutical Research* 7: 1010-1020.
- Achutha L, Parameshwar R, Madhava RB, Babu H (2013) Microwave-assisted synthesis of some quinoxaline-incorporated schiff bases and their biological evaluation. *Journal of Chemistry* 578438: 1-5.
- Bailly C, Echepare S, Gago F, Waring M (1999) Recognition elements that determine affinity and sequence-specific binding DNA of 2QN a biosynthetic bis quinoxaline analogue of echinimycin. *Anti-Cancer Drug Descriptions* 15: 291-303.
- Burguete A, Pontiki E, Litina DH, Vicente E, Solano B (2007) Synthesis and anti inflammatory/antioxidant activities of some new ring substituted 3-phenyl-1-(1,4-di-N-oxide-quinoxalin-2-yl)-2-propen-1-one derivatives and their 4,5-dihydro-(1H)-pyrazole analogues. *Bioorganic and Medicinal Chemistry Letters* 17: 6439-6443.
- Beheshtiha YS, Heravi MM, Saeedi M, Karimi N, Zakeri M, et al. (2010) Brønsted Acid Ionic Liquid [(CH₂)₂SO₃HMIM][HSO₄] as Novel Catalyst for One-Pot Synthesis of Hantzsch Polyhydroquinoline Derivatives. *Synthetic Communications* 40: 1216-1220.
- Chen P, Arthur MD, Derek N, Henry HG, Steven HS, et al. (2004) Imidazoquinoxaline Src-Family Kinase p56Lck Inhibitors: SAR, QSAR, and the Discovery of (S)-N-(2-Chloro-6-methylphenyl)-2-(3-methyl-1-piperazinyl)imidazo-[1,5-a]pyrido[3,2-e]pyrazin-6-amine as a Potent and Orally Active Inhibitor with Excellent in Vivo. *Journal of Medicinal Chemistry* 47: 4517-4529.
- Deepika Y, Nath PS (2012) Design, Synthesis of Novel quinoxaline derivatives and their antinoceptive activity. *Asian Journal of Pharmaceutical and Health Sciences* 2: 261-264.
- Wagle S, Adhikari A, Kumari N (2008) Synthesis of some new 2-(3-methyl-7-substituted-2-oxoquinoxaliny)-5-(aryl)-1,3,4-oxadiazoles as potential non-steroidal anti-inflammatory and analgesic agents. *Indian Journal of Chemistry* 47: 439-448.

15. Rajitha G, Saideepa N, Praneetha P (2011) Synthesis and evaluation of N-(*x*-benzamido cinnamoyl)-aryl hydrazone derivatives for anti-inflammatory and antioxidant activities. *Indian Journal of Chemistry and Biology* 50: 729-733.
16. Michael JW, Ben-Hadda T, Kchevan AT, Ramdani A, Touzani R, et al. (2002) 2,3-bifunctionalized quinoxalines: Synthesis, DNA Interactions and Evaluation of anticancer, anti-tuberculosis and anti-fungal activity. *Molecules* 7: 641-656.
17. Lindsley CW, Zhao Z, Leister WH, Robinson RG, Barnett SG, et al. (2005) Allosteric Akt (PKB) inhibitors: discovery and SAR of isozyme selective inhibitors. *Bioorganic and Medicinal Chemistry Letters* 15: 761-764.
18. Geefhavani M, Reddy J, Sathyanarayana S (2012) Synthesis, Antimicrobial and wound healing activities of diphenyl quinoxaline derivatives. *International Journal of Pharmacy and Technology* 4: 4700-4710.
19. Rangisetty JB, Gupta CN, Prasad AL, Srinavas P, Sridhar N, et al. (2001) Synthesis of new arylaminoquinoxalines and their antimalaria activity in mice. *Journal of Pharmacology and Pharmacy* 53: 1409-1413.
20. Nikam SS, Cordon JJ, Ortwin DF (1999) Design and synthesis of novel quinoxaline 2,3-dione AMPA/GlyN receptor antagonists. *Journal of Medicinal Chemistry* 42: 2266-2271.
21. Sridevi CH, Balaji K, Naidu A (2010) Antimicrobial Evaluation and Synthesis of Some Phenylpyrazolo benzothiazoloquinoxaline Derivatives. *E-Journal of Chemistry* 7: 234-238.
22. Urquiola C, Vieites M, Aguirre G (2006) Improving anti-trypanosomal activity of 3-aminoquinoxaline-2-carbonitrile N1,N4-dioxide derivatives by complexation with vanadium. *Bioorganic and Medicinal Chemistry* 14: 5503-5509.
23. Zarranz B, Jaso M, Lima LM (2006) Antiplasmodial activity of 3-trifluoromethyl-2-carbonylquinoxaline di-N-oxide derivatives. *Rev Bras Cienc Farm* 42: 55-57.
24. Xia H, Wang F, YU K (2005) Novel cyclophilin D inhibitors derived from quinoxaline exhibit highly inhibitory activity against rat mitochondrial swelling and Ca²⁺ uptake/release. *Acta Pharmacologica Sinica* 26: 1201-1211.
25. Dell A, William DH, Morris HR, Smith GA, Feeney J, et al. (1975) Structure revision of the antibiotic echinomycin. *Journal of American Chemical Society* 97: 2497-2501.
26. Sato S, Shiratori O, Katagiri K (1967) The mode of action of quinoxaline antibiotics. Interaction of quinomycin A with deoxyribonucleic acid. *Journal of Antibiotics* 20: 270-277.
27. Srinivas C, Sesha C, Kumar S (2007) Efficient, convenient and reusable polyaniline sulfate salt catalyst for the synthesis of quinoxaline derivatives. *Journal of Molecular Catalysis* 34: 227-230.
28. Weinstock M, Groner E (2008) Rational design of a drug for Alzheimer's disease with cholinesterase inhibitory and neuroprotective activity. *Chem-Biol Interact* 175: 216-221.
29. Mesulam M, Guillozet A, Shaw P, Quinn B (2002) Widely spread butyrylcholinesterase can hydrolyse acetylcholine in the normal and Alzheimer brain. *Neurobiol Dis* 9: 88-93.
30. Shah RS, Lee HG, Zhu X, Perry G, Smith MA (2008) Current approaches in the treatment of Alzheimer's disease. *Biomed Pharmacother* 62: 199-207.
31. Martinez A, Castro A (2006) Novel cholinesterase inhibitors as future effective drugs for the treatment of Alzheimer's disease. *Expert Opin Investig Drugs* 15: 1-12.
32. Cokugras AN (2003) Butyrylcholinesterase: Structure and physiological importance. *Turk J Biochem* 28: 54-61.
33. Guillozet A, Smiley JF, Mash DC, Mesulam MM (1997) Butyrylcholinesterase in the life cycle of amyloid plaque. *Ann Neurol* 42: 900-918.
34. Greig NH, Utsuki T, Ingram DK, Wang Y, Pepeu G, et al. (2005) Selective butyrylcholinesterase inhibition elevates brain acetylcholine, augments learning and lowers Alzheimer α -amyloid peptide in rodent. *PNAS* 102: 17213-17218.
35. Cheon HG, Lee CM, Kim BT, Hwangb KJ (2004) Lead discovery of quinoxalinediones as an inhibitor of dipeptidyl peptidase-IV (DPP-IV) by high-throughput screening. *Bioorganic and Medicinal Chemistry Letters* 14: 2661-2665.

Citation: Taiwo FO, Obuotor EM, Olawuni IJ, Ikechukwu DA, Iyiola TO (2017) Design, Synthesis and Biological Evaluation of Some Novel 3-Methylquinoxaline-2-Hydrazone Derivatives. *Organic Chem Curr Res* 6: 181. doi: [10.4172/2161-0401.1000181](https://doi.org/10.4172/2161-0401.1000181)

OMICS International: Publication Benefits & Features

Unique features:

- Increased global visibility of articles through worldwide distribution and indexing
- Showcasing recent research output in a timely and updated manner
- Special issues on the current trends of scientific research

Special features:

- 700+ Open Access Journals
- 50,000+ editorial team
- Rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at major indexing services
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsonline.org/submit>